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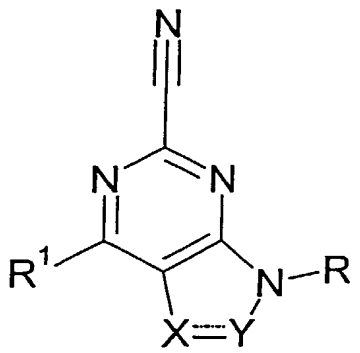
(54) Title: NOVEL PURINE- OR PYRROLOL[2,3-d]PYRIMIDINE-2-CARBONITILES FOR TREATING DISEASES ASSOCIATED WITH CYSTEINE PROTEASE ACTIVITY



(I)

(57) Abstract: The present invention therefore provides a compound of formula (I) and compositions for treating diseases associated with cysteine protease activity. The compounds are reversible inhibitors of cysteine proteases S, K, F, L and B. Of particular interest are diseases associated with Cathepsin S. In addition this invention also discloses processes for the preparation of such inhibitors.

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Novel purine- or pyrrolo[2,3-d]pyrimidine-2-carbonitiles for treating diseases associated with cysteine protease activity.

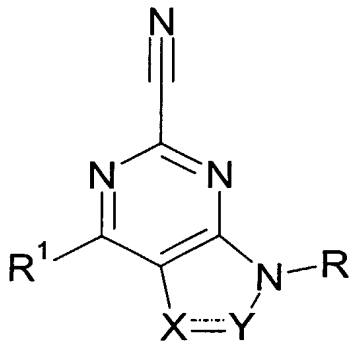
The present invention relates to compounds and compositions for treating diseases associated with cysteine protease activity. The compounds are reversible inhibitors of cysteine proteases S, K, F, L and B. Of particular interest are diseases associated with Cathepsin S. In addition this invention also discloses processes for the preparation of such inhibitors.

BACKGROUND OF THE INVENTION

Cathepsin S is a member of the papain superfamily of cysteine proteases which also encompasses Cathepsins B, H, L, O and K. Cathepsin S plays a key role in the processing of invariant chain in MHC class II complexes allowing the complex to associate with antigenic peptides. MHC class II complexes are then transported to the surface of the cell for presentation to effector cells such as T cells. The process of antigen presentation is a fundamental step in initiation of the immune response. In this respect inhibitors of cathepsin S could be useful agents in the treatment of inflammation and immune disorders such as, but not limited to, asthma, rheumatoid arthritis, multiple sclerosis and Crohn's disease. Cathepsin S has also been implicated in a variety of other diseases involving extracellular proteolysis such as the development of emphysema in COPD through degradation of elastin and in Alzheimers disease.

Other Cathepsins notably K and L have been shown to degrade bone collagen and other bone matrix proteins. Inhibitors of these cysteine proteases would be expected to be useful in the treatment of diseases involving bone resorption such as osteoporosis.

The present invention therefore provides a compound of formula (I)



(I)

in which:
X is N, NH, :CH or CH_2;
Y is N, :CH, CO, CH_2 or :CNR^2R^3, where R^2 and R^3 are independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R is aryl or heteroaryl optionally substituted by halogen, amino, hydroxy, cyano, nitro, trifluoromethyl, carboxy, $CONR^5R^6$, $SO_2NR^5R^6$, SO_2R^4, $NHSO_2R^4$, $NHCOR^4$, ethylenedioxy, methylenedioxy, C_{1-6} alkyl, C_{1-6} alkoxy, SR^4 or NR^5R^6 where R4 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, R^5 and R^6 are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR^4 group;
or R is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl both of which can optionally contain one or more O, S or NR^4 groups,

R^1 is a group $Y(CH_2)pR^7$ where p is 0, 1 or 2 and Y is O or NR^8 where R^8 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;
and R^7 is a 5- or 6-membered saturated ring containing one or more O, S or N atoms, aryl or a heteroaryl group containing one to four heteroatoms selected from O, S or N, the saturated ring, aryl and heteroaryl groups all being optionally substituted by halogen, amino, hydroxy, cyano, nitro, trifluoromethyl, carboxy, $CONR^5R^6$, $SO_2NR^5R^6$, SO_2R^4, $NHSO_2R^4$, $NHCOR^4$, C_{1-6} alkyl, C_{1-6} alkoxy, SR^4 or NR^5R^6 where R4 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, R^5 and R^6 are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR^4 group;

or R^1 is a group NR^9R^{10} where R^9 and R^{10} are independently hydrogen or C_{1-6} alkyl optionally containing one or more O, S or NR^4 groups, or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 5 or 6-membered saturated ring optionally containing a further O, S or N atom and optionally substituted by NR^9R^{10}, CO_2C_{1-6} alkyl, $CONR^{11}R^{12}$ where R^{11} and R^{12} are independently hydrogen or C_{1-6} alkyl, aryl or heteroaryl group optionally substituted by halogen, amino, hydroxy, cyano, nitro, trifluoromethyl, carboxy, $CONR^5R^6$, $SO_2NR^5R^6$, SO_2R^4, $NHSO_2R^4$, $NHCOR^4$, C_{1-6} alkyl, C_{1-6} alkoxy, SR^4 or NR^5R^6 where R4 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, R^5 and R^6 are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR^4 group; and pharmaceutically acceptable salts or solvates thereof.

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear or branched. Aryl groups include phenyl and naphthyl. Heteroaryl groups include 5- or 6-membered, 5,6- or 6,6-fused aromatic rings containing one or more heteroatoms selected from N, S, O. Examples include pyridine, pyrimidine, pyrazine, pyridazine thiazole, oxazole, pyrazole, imidazole, furan and thiophene, quinoline, isoquinoline, benzimidazole, benzofuran, benzothiophene, indole.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

Preferably X is N and Y is :CH, X and Y are:CH or X and Y are CH_2

Preferably R is C_{1-4}alkyl, or phenyl substituted by halogen, in particular chloro, SO_2Me, C_{1-6}alkoxy, in particular methoxy, C_{1-4}alkyl, in particular methyl or propyl.

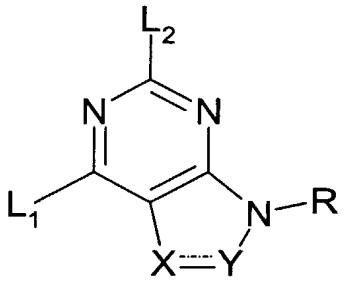
Preferably R^1 is a group $Y(CH_2)pR^7$ where p is 0 and Y is NR^8 where R^8 is hydrogen and R^7 is substituted phenyl. Preferably R^7 is phenyl substituted by halogen, especially chloro; or R^1 is NR^9R^{10} where R^9 and R^{10} are hydrogen or C_{1-3} alkyl or together with the nitrogen atom to which they are attached form a 5 or 6-membered saturated ring optionally containing a O, S or NR^4.

Preferred compounds of the invention include:
1-[9-(4-Chlorophenyl)-2-cyano-9H-purin-6-yl]-L-prolinamide,
9-(4-Chlorophenyl)-6-(4-pyrrolidin-1-ylpiperidin-1-yl)-9H-purine-2-carbonitrile,
9-(4-Chlorophenyl)-6-[(3-pyrrolidin-1-ylpropyl)amino]-9H-purine-2-carbonitrile,
6-(4-Aminopiperidin-1-yl)-9-(4-chlorophenyl)-9H-purine-2-carbonitrile,
6-[(2-Aminoethyl)amino]-9-(4-chlorophenyl)-9H-purine-2-carbonitrile,
9-(4-Chlorophenyl)-6-(dimethylamino)-9H-purine-2-carbonitrile,
9-(4-Methylphenyl)-6-pyrrolidin-1-yl-9H-purine-2-carbonitrile,
9-(4-Methoxyphenyl)-6-pyrrolidin-1-yl-9H-purine-2-carbonitrile,
9-(4-chlorophenyl)-6-pyrrolidin-1-yl-9H-purine-2-carbonitrile,
9-(4-Chlorophenyl)-6-(ethylamino)-9H-purine-2-carbonitrile,
tert-Butyl 4-[9-(4-chlorophenyl)-2-cyano-9H-purin-6-yl]piperazine-1-carboxylate,
9-(4-Chlorophenyl)-6-piperazin-1-yl-9H-purine-2-carbonitrile,
9-(2-Chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile
9-(3,4-Difluorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
9-(4-Isopropylphenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
9-(4-Methoxyphenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
9-(3-Chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
9-[4-(Methylsulfonyl)phenyl]-6-morpholin-4-yl-9H-purine-2-carbonitrile,
6-[(4-Chlorophenyl)amino]-9-ethyl-9H-purine-2-carbonitrile,
9-(4-Chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
8-Amino-6-[(4-chlorophenyl)amino]-9-ethyl-9H-purine-2-carbonitrile,
8-Amino-9-(4-chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
9-(4-Chlorophenyl)-6-morpholin-4-yl-8-oxo-8,9-dihydro-7H-purine-2-carbonitrile,
9-(4-Chlorophenyl)-8-(dimethylamino)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
7-(4-Chlorophenyl)-4-morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile,
7-(4-Chlorophenyl)-4-(ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-7-ethyl-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile,
1-[7-(4-Chlorophenyl)-2-cyano-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-L-prolinamide,
1-[2-Cyano-7-(4-methoxyphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-L-prolinamide,
7-(4-Methoxyphenyl)-4-pyrrolidin-1-yl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile,
7-(4-Methoxyphenyl)-4-morpholin-4-yl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile,

1-(4-Methylphenyl)-4-morpholin-4-yl-1H-pyrazolo[3,4-d]pyrimidine-6-carbonitrile, and pharmaceutically acceptable salts thereof.

The present invention further provides a process for the preparation of a compound of formula (I) which comprises

(i) reaction of a compound of general formula (II)

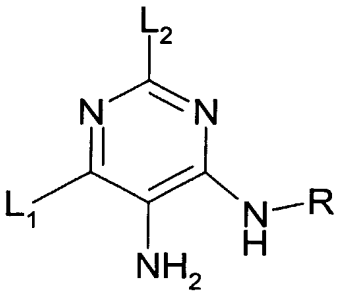


(II)

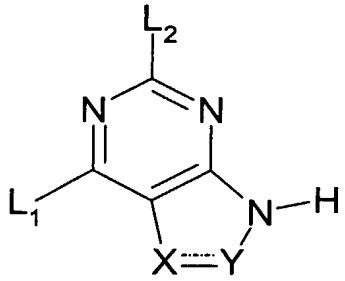
wherein L1 and L2 represent a leaving group (e.g. halide, sulphide, sulfoxide or sulphone group), preferably the sulphide is oxidised to a sulphoxide or sulphone group before displacement. An oxidising agent such as a peracid may be used, for example meta-chloroperbenzoic acid in dichloromethane at room temperature.

L1 may be displaced by R^1 where R^1 is defined in formula (I) and L2 may be displaced by cyanide, preferably using a salt (e.g. lithium, sodium or potassium cyanide). The sequence of displacement of L1, L2 may be varied.

Compounds of formula (II) where X=N and Y=:CH or :CNR^2R^3 may be prepared from compounds of formula (III) by ring cyclisations using, for example diethoxymethyl acetate, FMOC-NCS or R^3R^2NCSCl. Compounds of formula (II) where X=NH and Y=CO can also be prepared from compounds of formula (III) by reaction with phosgene or phosgene equivalent. The sequence of steps may also be varied, for example compounds of formula (III) may first have L1 and/or L2 displaced before the cyclisation step.



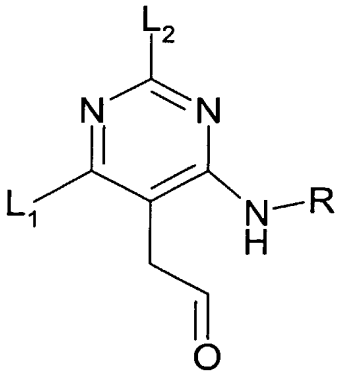
(III)



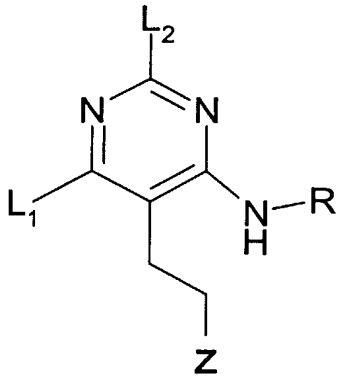
(IV)

Compounds of formula (II) may also be prepared from compound of formula (IV) by reaction with a group R-Z, where R is defined in formula (I) and Z is a leaving group (e.g. halide, activated alcohol).

Compounds of formula (II) where X and Y=:CH may also be prepared from compounds of formula (V) and compounds of formula (II) where X and Y = CH_2 may also be formed from compounds of formula (VI).



(V)



(VI)

According to a further feature of the invention there is provided a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, for use as a therapeutic agent.

According to a further feature of the present invention there is provided a method for producing inhibition of a cysteine protease in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, for use as a medicament; and the use of a compound of the formula **(I)** of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of a cysteine protease in a warm blooded animal, such as man. In particular the compounds of the invention are useful in the treatment of inflammation and immune disorders such as, but not limited to, asthma, rheumatoid arthritis, COPD, multiple sclerosis, Crohn's disease, Alzheimers and pain, such as neuropathic pain. Preferably the compounds of the invention are used to treat pain, especially neuropathic pain.

In particular the invention provides the use of a compound of the formula **(I)** of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of Cathepsin S in a warm blooded animal, such as man. In order to use a compound of the formula **(I)** or a pharmaceutically acceptable salt thereof for the therapeutic treatment of mammals including humans, in particular in the inhibition of a cysteine protease, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula **(I)** or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 100 mg and 1 g of the compound of this invention.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 1 $mgkg^{-1}$ to 100 $mgkg^{-1}$ of the compound, preferably in the range of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X.	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

The following examples illustrate the invention.

Example 1

1-[9-(4-Chlorophenyl)-2-cyano-9H-purin-6-yl]-L-prolinamide

(i) 6-Chloro-N~4~-(4-chlorophenyl)-2-(propylthio)pyrimidine-4,5-diamine
A mixture of 4-chloroaniline (5.33g), N,N-diisopropylethylamine (7.3ml) and 5-amino-4,6-dichloro-2-propylthiopyrimidine (10g) was heated at 100°C for 48h. The mixture was partitioned between ethyl acetate and water, the organics dried (MgSO4), and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 50% ethyl acetate in isohexane. Yield 4.6g

MS: APCI(+ve) 329(M+1)

(ii) 6-Chloro-9-(4-chlorophenyl)-2-(propylthio)-9H-purine
A solution of the product from step (i) (4.6g) in diethoxymethylacetate (25ml) was heated at 80°C for 8h. The mixture was added dropwise to a vigorously stirred mixture of water and isohexane (400ml, 1:1), and the solid filtered. The solid was purified by chromatography on silica eluting with 25% ethyl acetate in isohexane. Yield 2.8g

MS: APCI(+ve) 339(M+1)

(iii) 6-Chloro-9-(4-chlorophenyl)-2-(propylsulfonyl)-9H-purine
A mixture of the product from step (ii) (2.8g) and 3-chloroperoxybenzoic acid (3.6g, Aldrich 77% max.) in dichloroethane (40ml) was stirred at room temperature for 2h, washed with aqueous sodium metabisulphite solution, water, aqueous sodium hydrogencarbonate solution, water, dried (MgSO4) and evaporated under reduced pressure. Yield 2.5g

MS: APCI(+ve) 371 (M+1)

(iv) 1-[9-(4-Chlorophenyl)-2-cyano-9H-purin-6-yl]-L-prolinamide
A solution of the product from step (iii) (0.2g), L-prolinamide (0.062g) and N,N-diisopropylethylamine (0.19ml) in tetrahydrofuran (10ml) was stirred at room temperature for 24h. The solvent was removed, the residue dissolved in N,N-dimethylformamide (10ml) and sodium cyanide (0.05g) added and heated at 90°C for 10h. The mixture was

partitioned between ethyl acetate and water, the organics dried (MgSO4) and evaporated under reduced pressure. The residue was purified by RPHPLC. Yield 0.062g

MS: APCI(+ve) 368(M+1)
1H NMR: (DMSO-d6) δ 8.67(1H, s), 7.87-7.65(4H, 2xd), 6.95(2H, m), 4.08(2H, m), 2.97(1H, m), 2.33-1.96(4H, m).

Examples 2-12

Examples 2-12 were prepared according to the general method of example 1 using the appropriate amines.

Example 2

9-(4-Chlorophenyl)-6-(4-pyrrolidin-1-ylpiperidin-1-yl)-9H-purine-2-carbonitrile

MS: APCI(+ve) 408(M+1)
1H NMR: (DMSO-d6) δ 8.79-8.77(1H, s), 7.87-7.70(4H, 2xd), 2.52-2.49(8H, m), 2.38-2.32(1H, m), 2.01-1.43(8H, m)

Example 3

9-(4-Chlorophenyl)-6-[(3-pyrrolidin-1-ylpropyl)amino]-9H-purine-2-carbonitrile, trifluoroacetate salt

MS: APCI(+ve) 382(M+1)
1H NMR: (DMSO-d6) δ 9.46(1H, bs), 8.85-8.58(2H, 2xm), 7.89-7.71(4H, 2xd), 3.59-3.01(8H, m), 2.03-1.84(6H, m)

Example 4

6-(4-Aminopiperidin-1-yl)-9-(4-chlorophenyl)-9H-purine-2-carbonitrile, trifluoroacetate salt

MS: APCI(+ve) 354(M+1)
1H NMR: (DMSO-d6) δ 8.86-8.84(1H, s), 7.98-7.71(6H, 2xd+m), 3.49-3.30(5H, m), 2.12-1.50(4H, m)

Example 5

6-[(2-Aminoethyl)amino]-9-(4-chlorophenyl)-9H-purine-2-carbonitrile, acetate salt

MS: APCI(+ve) 314(M+1)
1H NMR: (DMSO-d6) δ 8.82(1H, s), 8.59(1H, m), 7.89-7.70(4H, 2xd), 3.94(2H, brm), 3.55-3.51(2H, t), 2.83-2.80(2H, t), 1.88(3H, s)

Example 6

9-(4-Chlorophenyl)-6-(dimethylamino)-9H-purine-2-carbonitrile

MS: APCI(+ve) 299(M+1)
1H NMR: (DMSO-d6) δ 8.80-8.79(1H, s), 7.88-7.69(4H, 2xd), 3.77(3H, m), 3.12(3H, m)

Example 7

9-(4-Methylphenyl)-6-pyrrolidin-1-yl-9H-purine-2-carbonitrile

MS: APCI(+ve) 305(M+1)
1H NMR: (DMSO-d6) δ 8.71(1H, s), 7.68-7.42(4H, 2xd), 4.15-4.12(2H, t), 3.69-3.65(2H, t), 2.40(3H, s), 2.08-1.93(4H, m)

Example 8

9-(4-Methoxyphenyl)-6-pyrrolidin-1-yl-9H-purine-2-carbonitrile

MS: APCI(+ve) 321(M+1)
1H NMR: (DMSO-d6) δ 8.66(1H, s), 7.69-7.15(4H, 2xd), 4.15-4.12(2H, t), 3.84(3H, s), 3.68-3.65(2H, t), 2.06-1.93(4H, m)

Example 9

9-(4-chlorophenyl)-6-pyrrolidin-1-yl-9H-purine-2-carbonitrile

MS: APCI(+ve) 325(M+1)
1H NMR: (DMSO-d6) δ 8.08(1H, s), 7.65(2H, d), 7.54(2H, d), 4.21(2H, t), 3.79(2H, t), 2.16-2.09(2H, m), 2.05-1.99(2H, m)

Example 10

9-(4-Chlorophenyl)-6-(ethylamino)-9H-purine-2-carbonitrile

MS: APCI(-ve) 297(M-1)
1H NMR: (DMSO-d6) δ 8.80(1H, s), 8.63(1H, t), 7.88(2H, d), 7.72(2H, d), 3.57-3.50(2H, m), 1.21(3H, t)

Example 11

tert-Butyl 4-[9-(4-chlorophenyl)-2-cyano-9H-purin-6-yl]piperazine-1-carboxylate

MS: APCI(+ve) 440(M+1)
1H NMR: (CDCl3) δ 8.10(1H, s), 7.63(2H, d), 7.55(2H, d), 4.50-4.40(4H, brs), 3.62-3.59(4H, m), 1.51(9H, s)

Example 12

9-(4-Chlorophenyl)-6-piperazin-1-yl-9H-purine-2-carbonitrile

A solution of the product from example 11 (0.27g) in dichloromethane (10ml) and trifluoroacetic acid (5ml) was stirred at room temperature for 0.5h then evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 0.4% triethylamine/6% methanol in dichloromethane. Yield 0.06g

MS: APCI(+ve) 340(M+1)
1H NMR: (CDCl3) δ 8.08(1H, s), 7.63(2H, d), 7.54(2H, d), 4.60-4.00(4H, brs), 3.03(4H, t)

Example 13

9-(2-Chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile

(i) 4-[6-Chloro-5-nitro-2-(propylthio)pyrimidin-4-yl]morpholine

Morpholine (2.6g) was added dropwise to a stirred solution of 4,6-dichloro-5-nitro-2-propylthiopyrimidine (8g) and N,N-diisopropylethylamine (3.85g) in acetonitrile (70ml) at 0°C. After 1h the solvent was evaporated and the residue partitioned between ethyl acetate and water, the organics dried (MgSO4) and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 25% ethyl acetate in isohexane. Yield 7.1g

MS: APCI(+ve) 319(M+1)

(ii) N-(2-Chlorophenyl)-6-morpholin-4-yl-5-nitro-2-(propylthio)pyrimidin-4-amine

A mixture of the product from step (i) (1g), 2-chloroaniline (0.4g) and N,N-diisopropylethylamine (0.404g) in isopropylalcohol (12ml) was heated at 55°C for 14h. The mixture was cooled and the isopropylalcohol decanted off. Yield 0.82g

MS: APCI(+ve) 410(M+1)

(iii) N~4~-(2-Chlorophenyl)-6-morpholin-4-yl-2-(propylthio)pyrimidine-4,5-diamine

A mixture of the product from step (ii) (0.82g) and iron powder (1.2g) in glacial acetic acid (40ml) was stirred at room temperature until the starting material was consumed. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and aqueous sodium hydrogen carbonate solution. The organics were dried (MgSO4) and evaporated under reduced pressure. Crude yield 0.82g

MS: APCI(+ve) 380/2(M+1)

(iv) 9-(2-Chlorophenyl)-6-morpholin-4-yl-2-(propylthio)-9H-purine

A solution of the product from step (i) (0.82g) in diethoxymethylacetate (8ml) was heated at 80°C for 16h. The mixture was added dropwise to a vigorously stirred mixture of water and isohexane (300ml, 1:1), ethyl acetate added, the organic layer dried (MgSO4) and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 25% ethyl acetate in isohexane. Yield 0.42g

MS: APCI(+ve) 390/2(M+1)

(v) 9-(2-Chlorophenyl)-6-morpholin-4-yl-2-(propylsulfonyl)-9H-purine

A mixture of the product from step (iv) (2.8g) and 3-chloroperoxybenzoic acid (0.63g, Aldrich 77% max.) in dichloromethane (15ml) was stirred at room temperature for 5h, washed with aqueous sodium metabisulphite solution, water, aqueous sodium hydrogencarbonate solution, water, dried (MgSO4) and evaporated under reduced pressure. Crude yield 0.74g

MS: APCI(+ve) 422/4 (M+1)

(vi) 9-(2-Chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile

Sodium cyanide (0.086g) was added to a solution of the product from step (v) (0.74g) in dimethylsulphoxide (10ml) and heated at 60°C for 36h. The mixture was partitioned between ethyl acetate and brine, the organics washed with brine, dried (MgSO4) and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 16% ethyl acetate in toluene. Yield 0.152g

MS: APCI(+ve) 341(M+1)

1H NMR: (DMSO-d6) δ 8.69(1H, s), 7.80(1H, d), 7.73-7.60(3H, m), 3.78(4H, t).

Examples 14-18

Examples 14-18 were prepared according to the general method of example 13 using the appropriate amines.

Example 14

9-(3,4-Difluorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile

MS: APCI(+ve) 343(M+1)

1H NMR: (DMSO-d6) δ 8.83(1H, s), 8.06-8.01(1H, m), 7.79-7.71(2H, m), 3.77(4H, t)

Example 15

9-(4-Isopropylphenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile

MS: APCI(+ve) 349(M+1)
1H NMR: (DMSO-d6) δ 8.77(1H, s), 7.68(2H, d), 7.50(2H, d), 3.76(4H, t), 3.04-2.97(1H, m), 1.26(6H, d)

Example 16

9-(4-Methoxyphenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile

MS: APCI(+ve) 337(M+1)
1H NMR: (DMSO-d6) δ 8.73(1H, s), 7.67(2H, d), 7.16(2H, d), 4.20(4H, broad S), 3.85(3H, s), 3.76(4H, t)

Example 17

9-(3-Chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile

MS: APCI(+ve) 341(M+1)
1H NMR: (DMSO-d6) δ 8.87(1H, s), 7.98(1H, s), 7.85-7.82(1H, m), 7.68(1H, t), 7.62-7.59(1H, m), 4.25(4H, broad S), 3.77(4H, t)

Example 18

9-[4-(Methylsulfonyl)phenyl]-6-morpholin-4-yl-9H-purine-2-carbonitrile

MS: APCI(+ve) 385(M+1)
1H NMR: (DMSO-d6) δ 8.95(1H, s), 8.20(2H, d), 8.13(2H, d),4.80-3.90(4H, brs), 3.77(4H, t)

Example 19

6-[(4-Chlorophenyl)amino]-9-ethyl-9H-purine-2-carbonitrile

(i) 2-Chloro-N-(4-chlorophenyl)-9H-purin-6-amine
A mixture of 4-chloroaniline (1.35g) and 2,6-dichloropurine (1g) in n-butanol (15ml) was heated at 100°C for 3h. The precipitate was filtered off, partitioned between ethyl acetate and aqueous sodium hydroxide solution, the organics dried (MgSO4), and evaporated

under reduced pressure. The residue was triturated with ethyl acetate and filtered. Yield 1.04g

MS: APCI(+ve) 280/2(M+1)

(ii) 2-Chloro-N-(4-chlorophenyl)-9-ethyl-9H-purin-6-amine

A mixture of the product from step (i) (1.04g), potassium carbonate (1.025g) and ethyl iodide (0.637g) in N,N-dimethylformamide (15ml) was stirred vigorously at room temperature for 2h. The mixture was partitioned between ethyl acetate and water, the organics washed with water, dried (MgSO4) and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 2:1 ethyl acetate in isohexane. Yield 0.63g

MS: APCI(+ve) 308/310(M+1)

(iii) N-(4-Chlorophenyl)-9-ethyl-2-(methylthio)-9H-purin-6-amine

A mixture of the product from step (ii) (0.6g) and sodium thiomethoxide (0.45g) in dimethylsulphoxide (15ml) was heated at 110°C for 4h. The mixture was partitioned between ethyl acetate and water, the organics washed with water, dried (MgSO4) and evaporated under reduced pressure. Yield 0.45g

MS: APCI(+ve) 320/322(M+1)

(iv) N-(4-Chlorophenyl)-9-ethyl-2-(methylsulfonyl)-9H-purin-6-amine

A mixture of the product from step (iii) (0.45g) and 3-chloroperoxybenzoic acid (1.2g, Aldrich 77% max.) in ethanol (20ml) was stirred at room temperature for 4h, ethyl acetate was added, the mixturewashed with aqueous sodium metabisulphite solution, water, aqueous sodium hydrogencarbonate solution, water, dried (MgSO4) and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 4:1 ethyl acetate in isohexane. Yield 0.39g

MS: APCI(+ve) 352/4 (M+1)

(v) 6-[(4-Chlorophenyl)amino]-9-ethyl-9H-purine-2-carbonitrile

A mixture of the product from step (iv) (0.13g) and sodium cyanide (0.054g) in dimethylsulphoxide (3ml) was stirred at room temperature for 72h then partitioned

between ethyl acetate and water. The organic layer was washed with water, dried (MgSO4), evaporated under reduced pressure and the residue purified by chromatography on silica eluting with 2:1 ethyl acetate in isohexane. Yield 0.035g

MS: APCI(-ve) 297(M-1)
1H NMR: (DMSO-d6) δ 10.54(1H, s), 8.62(1H, s), 7.90(2H, d), 7.44(2H, d), 4.28(2H, q), 1.46(3H, t)

Example 20

9-(4-Chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile

(i) N-(4-Chlorophenyl)-6-morpholin-4-yl-5-nitro-2-(propylthio)pyrimidin-4-amine
Morpholine (1.31ml) was added dropwise to a stirred solution of 4,6-dichloro-5-nitro-2-thiopropyl pyrimidine (4g) and N,N-diisopropylethylamine (7ml) in dichloromethane (50ml) at 0°C. After 1h, 4-chloroaniline (1.9g) was added, the mixture stirred at room temperature for 24h, then heated under reflux for 24h. The mixture was partitioned between dichloromethane and 2M hydrochloric acid, the organics washed with water, dried (MgSO4) and evaporated under reduced pressure. Yield 5g

MS: APCI(+ve) 410/2 (M+1)

(ii) 4-[(4-Chlorophenyl)amino]-6-morpholin-4-yl-5-nitropyrimidine-2-carbonitrile
A mixture of the product from step (i) (5g) and 3-chloroperoxybenzoic acid (12g, Aldrich 77% max.) in dichloromethane (200ml) was stirred at room temperature for 2h, washed with aqueous sodium metabisulphite solution, water, aqueous sodium hydrogencarbonate solution, water, dried (MgSO4) and evaporated under reduced pressure. The solid was dissolved in dimethylsulphoxide (30ml), sodium cyanide (2g) added and stirred for 1h at room temperature. Water (500ml) was added and the solid filtered, washed with water, dried and the residue triturated with ether. Yield 1.7g

MS: APCI(+ve) 361/3 (M+1)

(iii) 5-Amino-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile
The product from step (ii) (1.7g) and 10% palladium on charcoal (0.2g) in ethyl acetate (300ml) was hydrogenated at 2Bar for 8h, filtered through celite and the solvent evaporated under reduced pressure. Yield 1.05g

MS: APCI(+ve) 329/331 (M+1)

(iv) 9-(4-Chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile

A solution of the product from step (iii) (0.35g) in diethoxymethylacetate (10ml) was heated at 80°C for 12h, water added and the precipitate filtered. The solid was purified by chromatography on silica eluting with 30-40% ethyl acetate in isohexane. Yield 0.26g

MS: ESI 341 (M+1)

1H NMR: (DMSO-d6) δ 8.84(1H, s), 7.86(2H, d), 7.72(2H, d), 3.78-3.75(4H, m), 4.3(4H, brs)

Example 21

8-Amino-6-[(4-chlorophenyl)amino]-9-ethyl-9H-purine-2-carbonitrile

A solution of 5-amino-4-[(4-chlorophenyl)amino]-6-(ethylamino)pyrimidine-2-carbonitrile (0.41g, prepared using the method of example 20) in acetonitrile (5ml) was added to a stirred solution of FMOC-NCS (0.44g) in acetonitrile (10ml) at 0°C. After 1h, diisopropylcarbodiimide (0.252g) was added, the mixture heated under reflux for 4h, cooled, piperazine (0.1g) added and stirred at room temperature for 3h. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and brine, the organics dried (MgSO4) and evaporated under reduced pressure. The solid was purified by chromatography on silica eluting with 2-4% methanol in dichloromethane. Yield 0.12g

MS: APCI(+ve) 314(M+1)
1H NMR: (DMSO-d6) δ 9.62(1H, s), 7.83(2H, d), 7.37(2H, d), 7.14(2H, s), 4.08(2H, q), 1.26(3H, t)

Example 22

8-Amino-9-(4-chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile

A mixture of the product from example 20 step (iii) (0.6g) and FMOC-NCS (0.613g) in dichloromethane was heated at 40°C for 10h. The mixture was cooled , 1,4-diisopropylcarbodiimide (0.422ml) was added, heated for 5h then piperidine (1ml) added and stirred at room temperature for 3h. The solvent was evaporated under reduced pressure, the residue triturated with ether and recrystallised form water and dimethylsulphoxide. Yield 0.344g

MS: APCI(+ve) 356/8(M+1)
1H NMR: (DMSO-d6) δ 7.68(2H, d), 7.52(2H, d), 6.97(2H, s), 4.15-4.08(4H, m), 3.73-3.71(4H, m)

Example 23

9-(4-Chlorophenyl)-6-morpholin-4-yl-8-oxo-8,9-dihydro-7H-purine-2-carbonitrile

Triphosgene (0.09g) was added to a mixture of the product from example 20 step (iii) (0.4g) and pyridine (0.4ml) in dichloromethane (30ml) and the mixture stirred at room temperature. After 1h more triphosgene (0.02g) was added, stirred for a further 1h, water added and the solid filtered. The solid was washed with water, diethylether and dried. Yield 0.14g

MS: APCI(-ve) 355/7(M-1)
1H NMR: (DMSO-d6) δ 11.90(1H, s), 7.66-7.61(4H, m), 3.73-3.71(4H, m), 3.62-3.59(4H, m)

Example 24

9-(4-Chlorophenyl)-8-(dimethylamino)-6-morpholin-4-yl-9H-purine-2-carbonitrile

A mixture of the product from example 20 step (iii) (0.2g) and dimethylthiocarbamoyl chloride (0.1g) in acetonitrile (15ml) was heated at 60°C for 6h. The precipitate was filtered, the filtrate evaporated under reduced pressure and the residue purified by chromatography on silica eluting with 40% ethyl acetate in isohexane. Yield 0.034g

MS: APCI(+ve) 384(M+1)

1H NMR: (DMSO-d6) δ 7.68(2H, d), 7.58(2H, d), 4.15(4H, brs), 3..75-3.72(4H, m), 2.76(6H, s)

Example 25

7-(4-Chlorophenyl)-4-morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile

(i) 5-Allyl-2,6-dichloro-N-(4-chlorophenyl)pyrimidin-4-amine

A mixture of 5-allyl-2,4,6-trichloropyrimidine (7g), 4-chloroaniline (4g) and potassium carbonate (4.27g) in ethanol (100ml) was stirred at room temperature for 24h. The mixture was partitioned between ethyl acetate and water, the organics dried (MgSO4), and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with isohexane/diethylether (2:1). Yield 5g

MS: APCI(+ve) 314 (M+1)

(ii) {2,4-Dichloro-6-[(4-chlorophenyl)amino]pyrimidin-5-yl}acetaldehyde

A solution of the product from step (i) (2g) in dichloromethane (40ml) was added to a solution of osmium tetroxide (1ml, 2.5% wt in isopropylalcohol) and 4-methylmorpholine N-oxide (1.12g) in dichloromethane (1ml). After stirring at room temperature for 24h the mixture was washed with water, aqueous sodium sulphite solution, dried (MgSO4) and evaporated under reduced pressure. The residue was dissolved in methanol (40ml), cooled to 0°C and lead tetraacetate (3.85g) added. After 1h the mixture was diluted with water, extracted with ethyl acetate, the organics dried (MgSO4) and evaporated under reduced pressure. Yield 2g

MS: APCI(+ve) 316 (M+1)

(iii) 2,4-Dichloro-7-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidine

A solution of the product from step (ii) (2g) and p-toluenesulfonic acid (catalytic) in methanol (30ml) was stirred at room temperature for 2h then evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with isohexane/diethylether (2:1). Yield 0.5g

MS: APCI(+ve) 298/300 (M+1)

(iv) 7-(4-Chlorophenyl)-2,4-bis(ethylsulfonyl)-7H-pyrrolo[2,3-d]pyrimidine

Sodium ethanethiolate (0.437g) was added to a solution of the product from step (iii) (0.5g) in dimethylsulphoxide (20ml), stirred at room temperature for 30min then partitioned between ethyl acetate and water. The organics were dried (MgSO4) and evaporated under reduced pressure. The residue was dissolved in dichloromethane (20ml), 3-chloroperoxybenzoic acid (1.5g, Aldrich 77% max.) added, the mixture stirred at room temperature for 2h, washed with aqueous sodium metabisulphite solution, water, aqueous sodium hydrogencarbonate solution, water, dried (MgSO4) and evaporated under reduced pressure. Crude yield 1g

MS: APCI(+ve) 414 (M+1)

(v) 7-(4-Chlorophenyl)-4-morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile

A mixture of the product from step (iv) (0.35g), morpholine (0.11ml) and N,N-diisopropylethylamine (0.22ml) in tetrahydrofuran (10ml) was stirred at room temperature for 24h. The mixture was partitioned between ethyl acetate and water, the organics dried (MgSO4) and evaporated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (10ml), sodium cyanide (0.083g) added and the mixture heated at 90°C for 10h. Water was added, the solid filtered off then purified by RPHPLC 25-95% acetonitrile in aqueous trifluoroacetic acid. Yield 0.075g

MS: APCI(+ve) 340 (M+1)

1H NMR: (DMSO-d6) δ 7.94-7.64(5H, m), 7.11(1H, m), 3.94-3.74(8H, m)

Example 26

7-(4-Chlorophenyl)-4-(ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile

The above named example was prepared according to the general method of example 25 using the appropriate amine.

MS: APCI(+ve) 298 (M+1)

1H NMR: (DMSO-d6) δ 8.26(1H, t), 7.81-7.63(5H, m), 6.95-6.94(1H, m), 3.55-3.49(2H, q), 1.25-1.21(3H, t)

Example 27

4-[(4-Chlorophenyl)amino]-7-ethyl-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile

(i) 4-Chloro-7-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine

Sodium hydride (0.44g, 60% dispersion in oil) was added portionwise to a stirred solution of 4-chloro-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine (2g) in N,N-dimethylformamide (30ml) at 0°C. After 0.75h, ethyl iodide (0.88ml) was added, the mixture stirred for 2h, quenched with water and partitioned between ethyl acetate and brine. The organics were washed with water, dried (MgSO4), evaporated under reduced pressure and the residue purified by chromatography on silica eluting with 15% ethyl acetate in isohexane . Yield 1.98g

MS: APCI(+ve) 228/230 (M+1)

(ii) N-(4-Chlorophenyl)-7-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

A solution of the product from step (i) (0.5g) and 4-chloroaniline (0.84g) in ethanol (10ml) was heated under reflux for 24h then the solvent evaporated under reduced pressure. The

residue was partitioned between ethyl acetate and 2M hydrochloric acid, the organics washed with water, dried (MgSO) and evaporated under reduced pressure. Yield 0.7g

MS: APCI(+ve) 319/321 (M+1)

(iii) N-(4-Chlorophenyl)-7-ethyl-2-(methylsulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

A mixture of the product from step (ii) (0.7g) and 3-chloroperoxybenzoic acid (1.38g, Aldrich 77% max.) in dichloromethane (30ml) was stirred at room temperature for 1h, washed with aqueous sodium metabisulphite solution, water, aqueous sodium hydrogencarbonate solution, water, dried (MgSO4) and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 50% ethyl acetate in isohexane . Yield 0.37g

MS: APCI(+ve) 351/3 (M+1)

(iv) 4-[(4-Chlorophenyl)amino]-7-ethyl-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile

Sodium cyanide (0.103g) was added to a solution of the product from step (iii) (0.37g) in dimethylsulphoxide (10ml) and heated at 90°C for 48h. The mixture was partitioned between ethyl acetate and water, the organics dried (MgSO4) and evaporated under reduced pressure. The residue was purified by RPHPLC eluting with 29-95% acetonitrile in aqueous trifluoroacetic acid. Yield 0.14g

MS: APCI(+ve) 298/300(M+1)

1H NMR: (DMSO-d6) δ 9.94(1H, s), 7.83(2H, d), 7.67(1H, d), 7.46(2H, d), 6.93(1H, d), 4.26(2H, q), 1.38(3H, t)

Mpt 183°C

Example 28

1-[7-(4-Chlorophenyl)-2-cyano-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-L-prolinamide

(i) Methyl 2-oxotetrahydrofuran-3-carboxylate

Cyclopropane-1,1-dicarboxylic acid (10g) in acetonitrile(200ml) was treated with triethylamine (43ml) and iodomethane (19ml) at room temperature. The solution was stirred for 2h then heated at 75°C for 16h. The solvent was removed under reduced pressure, the residue dissolved in water, extracted with ethyl acetate, dried($MgSO_4$) and evaporated to a brown oil (6.70g).

1H NMR: (CDCl3) δ 4.55-4.30(2H, m), 3.82(3H, s), 3.59-3.55(1H, m), 2.73-2.47(2H, m).

(ii) 5-(2-Hydroxyethyl)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione

A solution of the product from step (i) (6.70g) in absolute ethanol (70ml) was treated with thiourea (3.53g) and triethylamine (12.80ml). The mixture was heated at reflux for 16h, the solvent was removed under reduced pressure and the solid dissolved in water (100ml). The solution was acidified with conc. hydrochloric acid to pH2 and extracted with ethyl acetate. Continuous extraction of the aqueous layer with dichloromethane for 80h gave a brown solid (2.20g).

MS: APCI(+ve) 189(M+1)

(iii) 5-(2-Hydroxyethyl)-2-(methylthio)pyrimidine-4,6(1H,5H)-dione

A solution of the product of step (ii) (2.2g) in methanol(10ml) was added to a solution of sodium (0.27g) in methanol (90ml). Iodomethane (0.73ml) was added and the mixture heated at reflux for 1 hour. The solvent was removed under reduced pressure to give a solid.

MS: APCI(+ve) 203(M+1)

(iv) 4,6-Dichloro-5-(2-chloroethyl)-2-(methylthio)pyrimidine

The product from step (iii) and phosphorus oxychloride (30ml) was heated at 100°C for 3h. The excess reagent was removed under reduced pressure, the residue quenched with ice-water, extracted with ethyl acetate, dried($MgSO_4$) and evaporated to an oil. The oil was purified by chromatography on silica eluting with isohexane:diethylether(4:1) to give a brown oil (0.36g).

MS: APCI(+ve) 257/259(M+1)

(v) 4-Chloro-7-(4-chlorophenyl)-2-(methylthio)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine

A solution of the product from step (iv) (0.36g) in acetonitrile (10ml) was treated with 4-chloroaniline (0.18g) and N,N-diisopropylethylamine (0.25ml). The mixture was heated at 150°C, the solvent evaporated to form a melt which solidified after heating for 90min. The solid was subjected to column chromatography eluting with isohexane:dichloromethane (1:1) to give a yellow solid (0.110g).

MS: APCI(+ve) 312(M+1)

(vi) 4-Chloro-7-(4-chlorophenyl)-2-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine

A mixture of the product from step (v) (0.11g) and 3-chloroperoxybenzoic acid (0.15g) in dichloromethane (20ml) was stirred at room temperature for 2h. The mixture was diluted with dichloromethane (100ml) and washed with sodium metabisulphite solution followed by sodium hydrogencarbonate solution, dried($MgSO_4$) and evaporated to an orange solid (0.1g).

MS: APCI(+ve) 344(M+1)

(vii) 4-Chloro-7-(4-chlorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile

A mixture of the product from step(vi) (0.1g) and sodium cyanide (0.022g) in dimethylsulfoxide(10ml) was stirred at room temperature for 2h. The mixture was partitioned between ethyl acetate and water, the organics separated, dried($MgSO_4$) and evaporated to a yellow solid (0.1g).

MS: APCI(+ve) 291(M+1)

(viii) 1-[7-(4-Chlorophenyl)-2-cyano-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-L-prolinamide

A mixture of the product from step (vii) (0.1g), L-prolinamide (0.039g) and N,N-diisopropylethylamine (0.09ml) in dimethylsulphoxide(10ml) was heated at 100°C for 8h. The mixture was partitioned between ethyl acetate and water, the organics separated, dried($MgSO_4$) and evaporated under reduced pressure. The residue was purified by reverse phase HPLC using 50 to 95% acetonitrile in 0.1% ammonium acetate buffer to yield a white solid (0.03g)

MS: APCI(+ve) 369(M+1)

1H NMR: (DMSO-d6) δ 7.72-7.02 (6H, m), 4.52-3.36 (7H, m), 2.14-1.90 (4H, m).

Examples 29-32

Examples 29-32 were prepared according to the method of example 28 steps(vi)-(viii).

Example 29

1-[2-Cyano-7-(4-methoxyphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-L-prolinamide

MS: APCI(+ve) 365(M+1)

1H NMR: (DMSO-d6) δ 7.55-6.95 (6H, m), 4.51-3.67 (8H, m), 3.49-3.40 (2H, m), 2.13-1.89 (4H, m).

Example 30

7-(4-Methoxyphenyl)-4-pyrrolidin-1-yl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile

MS: APCI(+ve) 322(M+1)

1H NMR: (DMSO-d6) δ 7.55-6.94 (4H, m), 3.99-3.38 (11H, m), 1.89-1.85 (4H, m).

Example 31

7-(4-Methoxyphenyl)-4-morpholin-4-yl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile

MS: APCI(+ve) 338(M+1)

1H NMR: (DMSO-d6) δ 7.55-7.51 (2H, d), 6.99-6.96 (2H, d), 4.04-3.60 (13H, m), 3.33-3.28 (2H, m).

Example 32

1-(4-Methylphenyl)-4-morpholin-4-yl-1H-pyrazolo[3,4-d]pyrimidine-6-carbonitrile

MS: APCI(+ve) 321(M+1)

1H NMR: (DMSO-d6) δ 8.71 (1H, s), 7.89-7.87 (2H, d), 7.42-7.39 (2H, d), 4.04-3.97 (4H, m), 3.80-3.77 (4H, m).2.39 (3H, s).

Measurement of Cathepsin S activity.

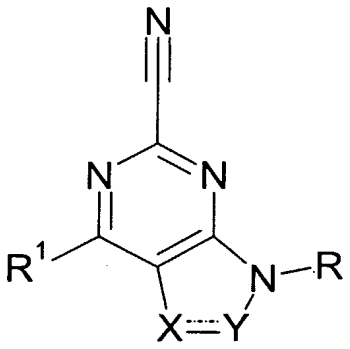
QFRET Technology (Quenched Fluorescent Resonance Energy Transfer) was used to measure the inhibition by test compounds of Cathepsin S-mediated cleavage of the synthetic peptide Z-Val-Val-Arg-AMC. Compounds were screened at five concentrations in duplicate and the pIC_{50} values reported.

Synthetic substrate, 20μM [final]Z-Val-Val-Arg-AMC in phosphate buffer were added to a 96 well black Optiplate. The assay plates were pre-read for compound auto fluorescence on SpectraMax Gemini at 355nM excitation and 460nM emission. 250pM [final] rHuman Cathepsin S in phosphate buffer was added and incubated for 2h at room temperature on the SpectraMax Gemini, taking readings every 20min at 355nM excitation and 460nM emission.

Activity Based template (5PTB-8) used the auto fluorescent corrected data to calculate the percentage inhibition for each compound concentration using the relevent plate controls. This data was used to construct inhibition curves and pIC_{50} estimated by non-linear regression using a 4 parameter logistic model.

CLAIMS

1. A compound of formula (I):



(I)

in which:
X is N, NH, :CH or CH_2;
Y is N, :CH, CO, CH_2 or :CNR^2R^3, where R^2 and R^3 are independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R is aryl or heteroaryl optionally substituted by halogen, amino, hydroxy, cyano, nitro, trifluoromethyl, carboxy, $CONR^5R^6$, $SO_2NR^5R^6$, SO_2R^4, $NHSO_2R^4$, $NHCOR^4$, ethylenedioxy, methylenedioxy, C_{1-6} alkyl, C_{1-6} alkoxy, SR^4 or NR^5R^6 where R4 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, R^5 and R^6 are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR^4 group;
or R is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl both of which can optionally contain one or more O, S or NR^4 groups,

R^1 is a group $Y(CH_2)pR^7$ where p is 0, 1 or 2 and Y is O or NR^8 where R^8 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;
and R^7 is a 5- or 6-membered saturated ring containing one or more O, S or N atoms, aryl or a heteroaryl group containing one to four heteroatoms selected from O, S or N, the saturated ring, aryl and heteroaryl groups all being optionally substituted by halogen,

amino, hydroxy, cyano, nitro, trifluoromethyl, carboxy, $CONR^5R^6$, $SO_2NR^5R^6$, SO_2R^4, $NHSO_2R^4$, $NHCOR^4$, C_{1-6} alkyl, C_{1-6} alkoxy, SR^4 or NR^5R^6 where R4 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, R^5 and R^6 are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR^4 group;

or R^1 is a group NR^9R^{10} where R^9 and R^{10} are independently hydrogen or C_{1-6} alkyl optionally containing one or more O, S or NR^4 groups, or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 5 or 6-membered saturated ring optionally containing a further O, S or N atom and optionally substituted by NR^9R^{10}, CO_2C_{1-6} alkyl, $CONR^{11}R^{12}$ where R^{11} and R^{12} are independently hydrogen or C_{1-6} alkyl, aryl or heteroaryl group optionally substituted by halogen, amino, hydroxy, cyano, nitro, trifluoromethyl, carboxy, $CONR^5R^6$, $SO_2NR^5R^6$, SO_2R^4, $NHSO_2R^4$, $NHCOR^4$, C_{1-6} alkyl, C_{1-6} alkoxy, SR^4 or NR^5R^6 where R4 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, R^5 and R^6 are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR^4 group;
and pharmaceutically acceptable salts or solvates thereof.

2. A compound according to claim 1 in which X is N and Y is :CH, X and Y are:CH or X and Y are CH_2

3. A compound according to claim 1 or 2 in which R is C_{1-4}alkyl, or phenyl substituted by halogen, SO_2Me, C_{1-6}alkoxy or C_{1-4}alkyl.

4. A compound according to any one of claims 1 to 3 in which R^1 is a group $Y(CH_2)pR^7$ where p is 0 and Y is NR^8 where R^8 is hydrogen and R^7 is substituted phenyl.

5. A compound according to any one of claims 1 to 3 in which R^1 is NR^9R^{10} where R^9 and R^{10} are hydrogen or C_{1-3} alkyl or together with the nitrogen atom to which they are attached form a 5 or 6-membered saturated ring optionally containing a O, S or NR^4.

6. A compound of formula (I) selected from:
1-[9-(4-Chlorophenyl)-2-cyano-9H-purin-6-yl]-L-prolinamide,
9-(4-Chlorophenyl)-6-(4-pyrrolidin-1-ylpiperidin-1-yl)-9H-purine-2-carbonitrile,
9-(4-Chlorophenyl)-6-[(3-pyrrolidin-1-ylpropyl)amino]-9H-purine-2-carbonitrile,
6-(4-Aminopiperidin-1-yl)-9-(4-chlorophenyl)-9H-purine-2-carbonitrile,

6-[(2-Aminoethyl)amino]-9-(4-chlorophenyl)-9H-purine-2-carbonitrile,
9-(4-Chlorophenyl)-6-(dimethylamino)-9H-purine-2-carbonitrile,
9-(4-Methylphenyl)-6-pyrrolidin-1-yl-9H-purine-2-carbonitrile,
9-(4-Methoxyphenyl)-6-pyrrolidin-1-yl-9H-purine-2-carbonitrile,
9-(4-chlorophenyl)-6-pyrrolidin-1-yl-9H-purine-2-carbonitrile,
9-(4-Chlorophenyl)-6-(ethylamino)-9H-purine-2-carbonitrile,
tert-Butyl 4-[9-(4-chlorophenyl)-2-cyano-9H-purin-6-yl]piperazine-1-carboxylate,
9-(4-Chlorophenyl)-6-piperazin-1-yl-9H-purine-2-carbonitrile,
9-(2-Chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile
9-(3,4-Difluorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
9-(4-Isopropylphenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
9-(4-Methoxyphenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
9-(3-Chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
9-[4-(Methylsulfonyl)phenyl]-6-morpholin-4-yl-9H-purine-2-carbonitrile,
6-[(4-Chlorophenyl)amino]-9-ethyl-9H-purine-2-carbonitrile,
9-(4-Chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
8-Amino-6-[(4-chlorophenyl)amino]-9-ethyl-9H-purine-2-carbonitrile,
8-Amino-9-(4-chlorophenyl)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
9-(4-Chlorophenyl)-6-morpholin-4-yl-8-oxo-8,9-dihydro-7H-purine-2-carbonitrile,
9-(4-Chlorophenyl)-8-(dimethylamino)-6-morpholin-4-yl-9H-purine-2-carbonitrile,
7-(4-Chlorophenyl)-4-morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile,
7-(4-Chlorophenyl)-4-(ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-7-ethyl-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile,
1-[7-(4-Chlorophenyl)-2-cyano-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-L-prolinamide,
1-[2-Cyano-7-(4-methoxyphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-L-prolinamide,
7-(4-Methoxyphenyl)-4-pyrrolidin-1-yl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile,
7-(4-Methoxyphenyl)-4-morpholin-4-yl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile,
1-(4-Methylphenyl)-4-morpholin-4-yl-1H-pyrazolo[3,4-d]pyrimidine-6-carbonitrile,
and pharmaceutically acceptable salts thereof.

7. A compound of formula (I) as defined in any one of claims 1 to 6 for use in therapy.

8. A compound of formula (I) as defined in any one of claims 1 to 6 for use in the treatment of pain.

9. A compound of formula (I) as defined in any one of claims 1 to 6 for use in the treatment of neuropathic pain.

10. A pharmaceutical composition which comprises a compound of the formula (I) as defined in any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

11. A method for producing inhibition of a cysteine protease in a mammal, such as man, in need of such treatment, which comprises administering to said mammal an effective amount of a compound as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof.

12. A method for treating pain, such as neuropathic pain, in a mammal, such as man, in need of such treatment, which comprises administering to said mammal an effective amount of a compound as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof.

13. Use of a compound of the formula (I) as defined in any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of Cathepsin S in a warm blooded animal, such as man.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01079

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 473/00, C07D 487/04, A61K 31/52, A61K 31/519, A61P 11/00, A61P 19/00, A61P 19/10, A61P 25/28. A61P 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 03020721 A1 (NOVARTIS AG ET AL), 13 March 2003 (13.03.03) --	1-13
A	WO 0232879 A1 (NAEJA PHARMACEUTICAL INC.), 25 April 2002 (25.04.02) --	1-13
A	WO 0055125 A2 (AXYS PHARMACEUTICALS, INC.), 21 Sept 2000 (21.09.00) --	1-13

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
24 Sept 2003

Date of mailing of the international search report
29 -09- 2003

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01079

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Week 200136 Derwent Publications Ltd., London, GB; Class B03, AN 2001-337719 & JP 20 01011037 A (KISSEI YAKUHIN KOGYO KK), 16 January 2001 (2001-01-16) abstract --	1-13
P,A	US 2002132819 A1 (CHESTER A. METCALF, III ET AL), 19 Sept 2002 (19.09.02) -- --------	1-13

INTERNATIONAL SEARCH REPORT

Interna application No.
PCT/SE03/01079

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11-12
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 11-12 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiced on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these (this) claim(s). The search has been based on the alleged effects of the compounds or compositions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01079

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03020721 A1	13/03/03	GB 0121033 D	00/00/00
WO 0232879 A1	25/04/02	AU 5057001 A	29/04/02
		CA 2426271 A	25/04/02
		EP 1326848 A	16/07/03
WO 0055125 A2	21/09/00	AU 3746100 A	04/10/00
		AU 3748600 A	04/10/00
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		BG 106013 A	31/05/02
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		BR 0009043 A	08/01/02
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		CA 2368148 A	21/09/00
		CN 1362947 T	07/08/02
		CN 1364155 T	14/08/02
		CZ 20013217 A	17/04/02
		CZ 20013248 A	17/04/02
		EE 200100485 A	17/02/03
		EE 200100487 A	17/02/03
		EP 1161415 A	12/12/01
		EP 1178958 A	13/02/02
		HR 20010737 A	31/10/02
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		JP 2002539192 T	19/11/02
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		NO 20014485 A	05/11/01
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		PL 350456 A	16/12/02
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		SK 12892001 A	04/06/02
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		TR 200103390 T	00/00/00
		TR 200201874 T	00/00/00
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		US 2003096796 A	22/05/03
		US 2003119788 A	26/06/03
		WO 0055126 A	21/09/00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01079

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2002103161 A	01/08/02
		WO 0144257 A	21/06/01
		WO 0144259 A	21/06/01
		WO 0144260 A	21/06/01